47. **(New)** The method of claim 31, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, and SEQ ID NO:8.

48. **(New)** The method of claim 31, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: LNLKEKP(X1)(X2)TPT(X3) and AAHRT(X4)SSR(X5)(X6)VR, wherein X1 is N or K, X2 is V or E, X3 is A or V, X4 is L or S, X5 is A or V, and X6 is A or V.

49. **(New)** The method of claim 31, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: LNLKEKPNVTPTAC and AAHRTSSSRAVVRC.

50. **(New)** The method of claim 28, wherein the antibody is polyclonal.

51. **(New)** The method of claim 28, wherein the antibody is monoclonal.--

## REMARKS

Claims 1-35 were pending in the present application. Claims 2-13, 15-23, 27, and 32-35 have been cancelled without prejudice herein. Claims 25, 26, 28, 29, and 31 have been amended. New claims 36-51 have been added. Accordingly, claims 1, 14, 24, 25, 26, 28-31, and 36-51 are currently pending. A marked-up version of the claims titled "Version Showing Changes Made" is attached as Appendix A.

Support for the amendments to the specification and claims and the new claims can be found in the application as filed and/or the claims as previously pending. Specifically, support for the amendment to claims 29 and 31 can be found at least at page 30, line 4. Support for claims 36 and 37 can be found at least at pages 29 and 30. Support for claim 38 can be found at

least in claim 5 as filed. Support for claims 39-41 can be found at least in claims 2-4 as filed, respectively. Support for claim 42 can be found at least in claim 7 as filed and at page 10, line 25. Support for claim 43 can be found at least in claim 8 as filed. Support for claims 44 and 45 can be found at least at page 12, line 18. Support for claims 46-49 can be found at least in claims 10-13 as filed, respectively. Support for claims 50 and 51 can be found at least at page 21. No new matter has been added.

Restriction Requirement

The Examiner required restriction among inventions I- XI. Applicants argued that the restriction requirement issued in the action of September 6, 2002 was improper because i) no objection as to lack of unity of invention was raised during the international phase of the application and it is improper under the PCT for national offices to require compliance with the requirements relating to the form or contents of the application different from or additional to those which are provided for in the PCT (Art 27 PCT) and ii) an allowable generic linking claim is present in the application.

The Examiner states that "Applicant has not addressed the observation that PCT Rule 13 does not provide for multiple products and methods." Applicants wish to make the following remarks of record. It is Applicants understanding that Rule 13 of the PCT provides that a group of inventions linked by special technical features (which define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art) shall be examined in an international application. Accordingly, multiple products and methods, linked by special technical features, are proper. The pending claims are all based on the special technical feature that Hepatitis C virus produces polypeptides in alternate reading frames, e.g., +1 and +2 to the standard open reading frame.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider the restriction requirement and the finality of the same.

Moreover, Applicants have presented an allowable generic claim, claim 31, which is generic to claims 28 and 29. Claim 31 is drawn to a method for diagnosing HCV infection comprising detecting the presence or absence of an HCV alternate reading frame polypeptide or detecting the presence or absence of antibodies which bind to an HCV alternate reading frame polypeptide in the body fluid or cells of a subject, wherein the presence of the HCV alternate reading frame polypeptide or antibodies which bind to the HCV alternate reading frame polypeptide is indicative of an infection with HCV. Claim 31 embraces the species of detecting HCV alternate reading frame polypeptides (claim 29) or antibodies that bind to such polypeptides (claim 28).

According to linking claim practice set forth in MPEP §§ 809 and 809.03, it is Applicants understanding that the linking claim (claim 31) will be examined with the invention elected and should the claim be allowed, the restriction requirement will be withdrawn. Applicants understand that the claims are currently being examined to the extent that they read on detection of HCV alternate reading frame polypeptides.

Rejection of claims 29 and 31 under 35 USC § 112, first paragraph.

Claim 29 has been rejected under 35 USC § 112, first paragraph as not conveying to one skilled in the art that the inventors had possession of the claimed invention. It is respectfully submitted that the language "isolated or recombinant" is not present in claim 29 as amended. Therefore, Applicants request that this rejection be withdrawn.

Claims 29 and 31 have been rejected as not being enabled. The Examiner states that:

> While the specification teaches that one can use such polypeptides to raise antibodies that may subsequently be used to detect

> polypeptides in tissue of body fluids of infected subjects (pages 20-25), the specification does not provide results of such assays that would serve to demonstrate that such polypeptides are actually circulating or present in the body fluids of infected subjects, or that antibodies raised against the disclosed polypeptides actually detect HCV +1 reading frame polypeptides in body fluids or tissues of infected subjects.

The Examiner further states that "[l]acking direct evidence that an HCV +1 reading frame polypeptide is present in the body fluid or tissue of an HCV infected subject, the specification cannot be said to enable one of skill in the art to practice the invention at the time the invention was made, without undue experimentation and with a reasonable expectation for success." This rejection is respectfully traversed.

Applicants point out that the Examiner appears to doubt the utility of the claimed invention for its stated purpose, rather than the doubting the ability of one of ordinary skill in the art to practice the claimed invention across its breadth. Given the teachings of the specification and the knowledge of one of ordinary skill in the art, the ordinarily skilled artisan could readily detect the presence or absence of a polypeptide comprising an amino acid sequence encoded by a hepatitis C alternate reading frame or antibodies that react with such a polypeptide in the body fluid or tissue of a subject. Exemplary means of detecting the presence of alternate reading frame polypeptides and antibodies reactive therewith are taught in the instant specification, e.g., at pages 29 and 30, and are well known in the art.

The Examiner has not set forth any evidence that would suggest that one of ordinary skill in the art would doubt the asserted utility of the claimed methods. Under 35 U.S.C. §112, first paragraph, the Examiner has the "initial burden of setting forth a reasonable explanation as to why the scope of protection provided by [the claims] is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Specifically, in *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995), it was held that:

> *Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.*

Additionally, the court stated that in the absence of a reason to doubt the objective truth of the teachings contained in the specification, the methods of making and using the claimed invention must be taken as complying with the requirements of §112, first paragraph. The Examiner has not met this burden, accordingly, the claims must be taken as complying with §112, first paragraph.

Rejection of claim 29 Under 35 USC § 112, second paragraph.

Claim 29 has been rejected under 35 USC § 112, second paragraph as lacking clarity. It is respectfully submitted that the language "isolated or recombinant" does not appear in claim 29 as amended. Reconsideration and withdrawal of this rejection is requested.

Rejection of claims 29 and 31 Under 35 USC § 103(a).

Claims 29 and 31 have been rejected under 35 USC § 103(a) as being unpatentable over either of Lo et al. (Virology 199:124-131, 1994; Ref B1) or Lo et al. (Virology 213:455-561, 1995; Ref B2) In light of Xu et al. (The EMBO Journal 20(14):3840-3848, 2001). This rejection is respectfully traversed.

The Examiner states that "[w]hile neither Lo B1 nor Lo B2 discloses the P16 [peptide] as being an HCV +1 reading frame polypeptide, both disclose it as a protein of interest in HCV infection and both disclose detecting it an immunoassay." The Examiner further states that "It would have been obvious to one of ordinary skill in the art at the time the invention was made to

have detected the HCV P16 of Lo B1 or Lo B2 in the body fluid or tissue of a subject by immunoassay and to correlate the presence of HCV P16 with the presence of HCV infection because both Lo B1 and Lo B2 disclose the HCV P16 as a polypeptide that is specifically associated with the expression of HCV core nucleotide sequence."

The Examiner also relies on the teachings of Xu et al. However, the Xu et al. reference was published in 2001, well after Applicants' priority date. Accordingly, the Xu reference is not available as prior art and cannot be used to provide the motivation to modify the teachings of the primary references.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Claims 28, 29, and 31 are directed to methods of diagnosing HCV infection comprising detecting the presence or absence of an HCV alternate reading frame polypeptide or detecting the presence or absence of antibodies which bind to an HCV alternate reading frame polypeptide in the body fluid or cells of a subject, wherein the presence of the HCV alternate reading frame

polypeptide or antibodies which bind to the HCV alternate reading frame polypeptide is indicative of an infection with HCV.

The LoB1 reference fails to teach or suggest the class of HCV alternative reading frame polypeptides presently being claimed. Lo B1 teaches that P16 is an HCV core gene product and is co-amino-terminal with the full length core protein, p21. The reference teaches that the synthesis of P16 either results from a premature termination of translation of the core protein or results from cleavage of the nascent polypeptide chain during translation (see, e.g., page 129, column 2, third full paragraph). Therefore, the Lo B1 reference teaches that P16 is a shortened form of the core protein. According to this teaching, p16 is encoded by the standard HCV reading frame which specifies the core protein and, therefore, is not an alternate reading frame polypeptide.

Moreover, the Lo B1 reference fails to teach or suggest methods of diagnosing HCV infection comprising detecting the presence or absence of an alternate reading frame polypeptide or an antibody reactive therewith. The reference does not teach that P16, regardless of whether or not it is an alternate reading frame polypeptide, is expressed in during the course of HCV infection at all. All of the data in the reference was generated using ***in vitro translation experiments***. In addition, the reference teaches that P16 is only detected in ***only one isolate*** tested, the HCV-1 isolate which has a Lys-9 residue. The limited expression of P16 taught in the reference ***teaches away*** from the use of P16 as a diagnostic.

The Lo B2 reference examines expression of plasmids comprising HCV core protein sequence in the presence or absence of its downstream E1 envelope protein sequence. The reference confirms the teaching of Lo B1 and states that P16 and P21 are co-amino-terminal. The amino terminal sequence of P16 is taught to be: XTNPKPQK$_9$KNKRNTN, identical to the P21 sequence (See Table 1). Therefore, the Lo B1 reference also teaches that P16 is a shortened

form of the core protein. According to this teaching, p16 is encoded by the standard HCV reading frame which specifies the core protein and, therefore, is not an alternate reading frame polypeptide.

Moreover, as in the case of the Lo B1 reference, the Lo B2 reference fails to teach or suggest methods of diagnosing HCV infection comprising detecting the presence or absence of an alternate reading frame polypeptide or antibodies reactive therewith. The reference looks at expression of P16 from artificial constructs and teaches that P16 is expressed from these constructs in *E. coli* and CV1 cells. However, expression of P16 is taught to be enhanced ***in the absence*** of the E1 envelope protein. In the case of infection with HCV, the E1 envelope protein is present. The reference does not examine the expression of P16 in the course of HCV infection and there is no indication in the reference that P16 is made during infection.

The Examiner has failed to set forth adequate evidence of a motivating force which would have *impelled* one of ordinary skill in the art to modify the teachings of the references to arrive at the claimed invention. In contrast to the teachings of the prior art, Applicants have shown that alternate reading frame polypeptides are produced during infection and that they are immunogenic. Applicants provide a working example in which alternate reading frame polypeptides were synthesized and sera from patients with HCV were tested for their reactivity with the polypeptides. These data show that HCV patient sera contained antibodies reactive with alternate reading frame polypeptides as well as with core polypeptides. In fact, the reactivity to alternate reading frame polypeptides was as good as or better than the reactivity to core polypeptides in some patients. Prior to Applicants invention, i) ***no one had identified alternate reading frame polypeptides having an amino acid sequence that differed from core***, ii) ***no one had shown that such polypeptides were produced during an infection in a human subject***, and iii) ***no one had shown that such polypeptides were immunogenic in a human subject.*** Absent

Applicants teachings, there was no motivation present in the art to diagnose HCV infection by detecting the presence or absence of a polypeptide comprising an amino acid sequence encoded by an HCV alternate reading frame or antibodies reactive therewith.

In addition, even if one of ordinary skill in the art would have been motivated to make the invention, which Applicants deny, there was no reasonable expectation of success that HCV could be diagnosed using an alternate reading frame polypeptide or antibodies reacting therewith. For example, as set forth above Lo B1 teaches that P16 was expressed by only one isolate and Lo B2 teaches that P16 expression was enhanced when E1 envelope, which is present in the HCV viral genome, was not present in the construct. Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in using the claimed methods to diagnose HCV infection.

Accordingly, the claims are not obvious in view of the art of record and it is respectfully requested that the rejection of claims 29 and 31 be reconsidered and withdrawn.

## CONCLUSION

If a telephone conversation with applicant's agent would expedite the prosecution of the above-identified application, the examiner is urged to call applicant's agent at (617) 227-7400.

Respectfully submitted,

Megan E. Williams
Registration No. 43,270
Attorney for Applicants

LAHIVE & COCKFIELD
28 State Street
Boston, MA 02109
(617) 227-7400

Dated: **March 20, 2003**

## VERSION SHOWING CHANGES MADE

28. **(Amended)** A method of diagnosing [HCV] Hepatitis C virus (HCV) infection comprising, detecting the presence or absence of antibodies in the body fluid of a subject, wherein the antibodies [which] react with [the] a polypeptide [of claim 1] comprising an amino acid sequence encoded by an HCV alternate reading frame [in the body fluid of a subject], and wherein the presence of the antibodies [which bind the polypeptide] is indicative of an infection with HCV.

29. **(Amended)** A method of diagnosing [HCV] Hepatitis C virus (HCV) infection, comprising detecting the presence or absence of [the] a polypeptide in the body fluid or cells of a subject, wherein the polypeptide comprises an amino acid sequence encoded by an HCV alternate reading frame [of claim 1 in the body fluid or tissue of a subject], and wherein the presence of [an] the [HCV] polypeptide is indicative of an infection with HCV.

31. **(Amended)** A method of diagnosing HCV infection comprising detecting the presence or absence of an HCV alternate reading frame polypeptide or detecting the presence or absence of antibodies which bind to an HCV alternate reading frame polypeptide in the body fluid or cells of a subject, wherein the presence of the HCV alternate reading frame polypeptide or antibodies which bind to the HCV alternate reading frame polypeptide is indicative of an infection with HCV.